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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,886	03/13/2000	David J. Grdina	P-01904US1	6435

7590 11/15/2004

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/523,886	GRDINA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 7, 9, 10, 12, 13, 23-31 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,9,10,12,13,23-31 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-30-04 has been entered.

Applicants' amendment filed 8-30-04 has been entered. Claims 1, 9, 10, 12, 13, 23, 30 and 31 have been amended. Claims 3-6, 11, 32 and 33 have been canceled. Claims 1, 7, 9, 10, 12, 13, 23-31 and 34 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 7, 9, 10, 12, 13, 23-31 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting or reducing the number of metastases in lung by administering WR-2721 at a concentration of 50mg/kg to 100mg/kg to an animal, does not reasonably provide enablement for reducing the number or inhibiting metastases in tissues other than lung or preventing metastases by administering WR-2721, or reducing the number of metastases by administering WR-2721 at a concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg to an animal. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 7, 9, 10, 12, 13, 23-29, and 34 are directed to a method for reducing the number of metastases in an animal having a primary tumor, such as a sarcoma or a carcinoma, by administering to said animal a WR-2721 at a concentration of 10mg/kg to 150mg/kg. Claims 9 and 10 specify the WR-2721 is the thiol form and disulfide form, respectively. Claim 12 specifies the route of administration is intravenous, intraperitoneal, intradermal, intramuscular, dermal, nasal, buccal, rectal, vaginal, inhalation, or topical. Claim 13 specifies the WR-2721 is formulated into solutions, suspensions, tablets etc. Claims 25-29 specify further monitoring the ability of the ability of the dose of the WR-2721 to reduce metastases via measuring the activity of matrix metalloproteinase (MMP), such as MMP-2 or MMP-9, the stimulation of angiostatin, or the stimulation of MnSOD gene expression. Claim 34 specifies the dose of WR-2721 is about 50mg/kg to 100mg/kg. Claims 30 and 31 are directed to a method for inhibiting or preventing metastases in an animal having a primary tumor by administering to said animal a dose of 10mg/kg to 150mg/kg of WR-2721.

The claims encompass using a WR-2721 at a dose of 10mg/kg to 150mg/kg to reduce the number of metastases, to inhibit metastases, or to prevent metastases at any target site in an animal (page 13). The specification only discloses inhibition of metastases of lung by using WR-2721, i.e. amifostine, at a concentration of 50mg/kg to 100mg/kg in C3Hf/Kam mice, which have been injected with sarcoma or adenocarcinoma tumor cells.

The specification fails to provide adequate guidance and evidence for reducing the number metastases or inhibiting metastases in tissues other than lung in an animal by

administering a WR-2721 at any concentration, or reducing the number of metastases or inhibiting metastases in lung by administering WR-2721 at a concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg to an animal via various administration rotues. The specification also fails to provide adequate guidance and evidence for preventing metastases at any location in an animal by administering WR-2721 at a dose of 10mg/kg to 150mg/kg.

The specification only discloses inhibition of metastases of lung by using WR-2721, i.e. amifostine, at a concentration of 50mg/kg to 100mg/kg. The occurrences of metastases result from various types of tumors at different locations or tissues in an animal rely on different mechanisms and pathobiologies. There is no evidence of record that WR-2721 can reduce the number of metastases or inhibit metastases of tissues or locations other than lung in an animal. Kanclerz et al., 1988 (IDS-C22, filed 9-8-00) states that "treatment with a single dose of WR-2721 (0.4g/kg) promoted lung metastases but exerted a suppressive effect on lymph node tumors. When the radioprotector was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) a slight enhancement of lung metastases and suppression of extrapulmonary metastases was observed" (e.g. abstract). Kanclerz also reports that misonidazole and SR-2508 promote lung metastases formation (e.g. abstract, p. 313, right column). Figure 4 of Kanclerz shows that 0.05g/kg (50mg/kg) and 0.1g/kg (100mg/kg) of WR-2721 do not inhibit metastases at sacral and paraaortic nodes and mediastinum in mice, and only significantly inhibit metastases in adrenals of mice. Therefore, doses and schedules of a compound administered to a subject and the type of tumors and location of metastases are important factors in determining the effect of said compound on metastases.

Further, Lesniak et al., 2001 (Current Neurology and Neuroscience Reports, Vol. 1, p. 210-216) points out that there are problems with drug delivery to malignant brain tumor, for example, the blood-brain barrier (BBB), blood-cerebrospinal fluid barrier (BCB) and a general lack of response to many chemotherapeutic agents (e.g. abstract). "The tight junctions between endothelial cells of the capillaries form a physiologic and pharmacologic barrier that prevents the influx of molecules from the bloodstream into the brain. In general, only small, electrically neutral, lipid-soluble molecules can penetrate this capillary endothelium, and many chemotherapeutic agents do not fall in this category" (e.g. p. 210, right column). The BCB can control the penetration of molecules within the interstitial fluid of the brain parenchyma and it can actively remove chemotherapeutic agents, such as methotrexate, from cerebrospinal fluid (CSF) (e.g. p. 210, right column). The specification fails to provide adequate guidance and evidence whether the WR-2721 molecule can penetrate the BBB or BCB barrier so as to reach the target site in the brain such that metastases in the brain can be reduced or inhibited. There is no evidence of record that WR-2721 can reduce the number of metastases or inhibit metastases at various types of brain tumors in the brain of an animal. Thus, it would be unpredictable at the time of the invention whether WR-2721 can reduce the number of metastases or inhibit metastases at locations other than lung in an animal and one skilled in the art at the time of the invention would not know how to use the WR-2721 to practice the full scope of the invention claimed.

The specification only discloses inhibition of metastases of lung by using WR-2721 at a concentration of 50mg/kg to 100mg/kg. A dose of WR-2721 at 200mg/kg does not inhibit spontaneous Sa-NH metastases formation (see Figure 1 of the present invention). Kanclerz

(1988, IDS-C22, filed 9-8-00) reports single dose of WR-2721 of 0.4g/kg promotes lung metastases, however, Milas et al., 1984 (IDS-C51) states that single dose of 400mg/kg WR-2721 greatly reduces radiation and CY-induced enhancement of metastases in the lung of mice. The specification fails to provide adequate guidance and evidence whether WR-2721 at a concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg can reduce the number of metastases at various locations in an animal. In view of the contradiction of the data regarding WR-2721 at a concentration of 400mg/kg (Kanclerz and Milas) and the lack of evidence of the activity of WR-2721 at a concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg, it would be unpredictable at the time of the invention whether WR-2721 at said concentration range can reduce the number of metastases at various locations in an animal. One skilled in the art the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

The specification also fails to provide adequate guidance and evidence for prevention of metastases of various tumors *in vivo* by using WR-2721. The specification discloses injection of WR-2721 **after** the injection of tumor cells into mice and Tables 1 and 2 show occurrence of spontaneous metastases and incidence of metastases for Sa-NH, MCak, and OCa tumors in mice. Preventing metastases in an animal means administration of the drug **before** infection or introduction of pathogen to said animal and said administration of the drug prevent the occurrence of metastases in said animal. Claim 31 encompasses preventing metastases of various types of tumors in an animal by administering to said animal a dose of 10mg/kg to 150mg/kg of WR-2721. Wattenberg, L., 1997 (Proceedings of the Society for Experimental Biology and Medicine, Vol. 216, No. 2, p. 133-141) reports that "a major problem that exist for

cancer prevention if that we do not know the cause of over 50% of cancers. Even when causes are known, serious difficulties often exist in removing them". "Chemoprevention is not simple, and successes may not come quickly" (e.g. abstract). Wattenberg points out that a major problem for studying chemoprevention of prostate cancer, ovarian cancer and small-cell lung carcinoma is a lack of experimental animal model for those cancers (e.g. p. 137, right column). There is no evidence of record that WR-2721 can prevent metastases of various types of cancers in an animal. Absent the efficacy of WR-2721 in preventing metastases of various types of cancers in an animal, one skilled in the art at the time of the invention would not know how to use the WR-2721 to prevent metastases of any cancer in an animal at a dose of 10mg/kg to 150mg/kg.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER